REMARKS

Claims 1-14 have been canceled without prejudice or disclaimer and claims 15-28 have been added. Claims 15-28 are presently pending in this application. The claims have support in the specification and claims as filed. The amendment to the specification on page 8, line 26, corrects an obvious typographical error in the citation of Sato *et al.*, already of record. No new matter has been added.

1. Specification

Applicants have amended the title to be descriptive and have amended the specification to recite the priority documents. It is believed that applicants have made the corrections as requested by the examiner.

2. Rejections under 35 U.S.C. § 112, second paragraph

Claims 11 and 14 (now claims 25 and 28) are rejected as indefinite for reciting the laboratory designation "PM-1" for the preferred monoclonal antibody of the present invention. Claims 11-14 have been canceled, however, new claims 25 and 28 that recite "PM-1" now designate the deposit accession number, FERM BP-2998. The hybridoma PM-1 was deposited as FERM BP-2998 on July 10, 1990, as an international deposit under the Budapest Treaty at the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology, 1-3, Higaski 1 chrome Tsukuba-shi Ibaraki-ken, 305, Japan. Applicants will provide documentation that the name "PM-1" corresponds to the FERM BP deposit number in the near future.

Claims 13 and 14 are rejected as indefinite for reciting " a reshaped human antibody" or "reshaped human PM-1 antibody." Applicants have canceled these claims and the new claims do not contain the term "reshaped" but claims 27 and 28 do recite "humanized." The specification on page 8, lines 26-29 references WO 92/19759 which discloses the production of several variations of a humanized PM-1 antibody.

Claim 12 (now claims 26) is rejected as indefinite for reciting "chimeric." This term is recited in claim 26 but is also defined as "a monoclonal antibody comprising the variable immunoglobulin heavy and light chains from a murine monoclonal antibody to an IL-6 receptor and the constant immunoglobulin heavy and light chains from a human monoclonal antibody."

Applicants believe that the language of claim 26 clearly defines what is intended by the term "chimeric antibody."

In view of the amendments to the claims and the deposit information provided, it is requested that these rejections should be withdrawn.

3. Rejections under 35 U.S.C. § 112, first paragraph

3.1 Claims 11 and 14 (now claims 25 and 28)

Claims 11 and14 are rejected as allegedly not being enabled because the specification does not provide evidence that the PM-1 hybridoma producing the PM-1 monoclonal antibody is known and readily available to the public or reproducible from the written description. As discussed above, PM-1 hybridoma was deposited on July 10, 1990 and is publicly available as deposit accession number FERM BP-2998. In view of this information, it is requested that this rejection be withdrawn.

3.2 Claims 1-14

Claims 1-14 are rejected because the specification does not enable the claimed pharmaceutical compositions for the prevention or treatment of the recited diseases. The claims are directed to a method of treating a subject having a disease caused by interleukin-6 (IL-6) production comprising administering a therapeutically effective amount of an antibody to an IL-6 receptor in a pharmaceutically acceptable carrier.

The examiner states that methods of using antibodies to IL-6 receptors for the prevention of disease caused by IL-6 production were not routinely known at the time of the invention. In support of her position, the examiner cites publications (Durum and Henderson) alleging that the treatment of diseases with an antibody to an IL-6 receptor is unpredictable. The examiner further cites publications by Gura *et al.* that she alleges support her position that there are "potential shortcomings of extrapolating from *in vitro* studies and animal studies to similar procedures in cancer patients." However Gura *et al.* is not directed to the claimed method of treatment and, therefore, should not be considered relevant against the present set of claims. The use and relevance of cancer therapy studies as predictive of clinical outcomes should not be extrapolated by the examiner to predict the relevance of animal models to support the claimed method of treatment.

In support of the pending set of claims, applicants herewith enclose in Appendix A, a 1997 publication in the *Japanese J. of Clinical Immunology* 20(2):87-94 and an English

translation that support the enablement of the pending method of treatment claims. This publication shows that the administration of IL-6 receptor antibodies to human subjects is useful in treating hyperimmuoglobulinemia, plasmacytosis and anemia. Additionally, applicants believe that Examples 2 and 3 in the specification support claim 23 directed to the treatment of subjects with cachexia.

Applicants believe that they have provided evidence to support the enablement of the pending set of claims through the use of the post-published 1997 publication and the examples in the specification. The 1997 publication provides evidence that the animal models in the specification were predictive and could be correlated to the outcome in humans. In view of the above arguments, it is requested that this rejection be withdrawn against the pending claims.

The examiner states that the two different animal models described in the specification demonstrating the effects of administering IL-6 receptor antibody are insufficient to demonstrate correlation to the outcome when treating humans. The examiner cites Strassmann *et al.* to support her position that the level and stability of human IL-6 in transgenic mice may not be comparable to the level and stability of IL-6 causing diseases in humans, and as such, the results in Example 1 of the present invention does not sufficiently enable the broadly claimed pharmaceutical compositions.

Applicants do not interpret the discussion of the role of cytokines in cachexia in Strassmann *et al.* to indicate that one could not correlate the outcome in transgenic mice with the outcome in humans. Applicants interpret this publication as generally discussing the effects of administering large amounts of cytokines. This publication does not discuss the lack of correlation between animal and human studies.

For all of the foregoing reasons, it is requested that this rejection be withdrawn against the pending claims.

4. Rejections under 35 U.S.C. § 102

Some or all of claims 1-14 are rejected as being anticipated by Sato *et al.*, (1993), Sato *et al.*, (1994), Hirata *et al.*, Tamura *et al.*, or Taetle *et al.* as disclosing pharmaceutical compositions comprising an antibody specific for an IL-6 receptor. Sato *et al.*, (1993), Sato *et al.*, (1994), and Hirata *et al.* are also applied as allegedly showing that the applicant did not invent the claimed subject matter (pharmaceutical compositions).

The claims to the pharmaceutical composition have been canceled and the only claims pending are method of treatment claims. The above cited publications do not disclose a method of treating a subject having a disease caused by interleukin-6 (IL-6) production comprising administering to a subject a therapeutically effective amount of an antibody to an IL-6 receptor in a pharmaceutically acceptable carrier. None of these publications disclose animal models supporting the utility of administering an antibody to an IL-6 receptor. Clearly, statements of intended clinical use in the prior art made in the absence of animal model data would be insufficient to give one of ordinary skill in the art a reasonable expectation of success. For these reasons, it is requested that all of the rejections under 35 U.S.C. § 102 be withdrawn.

5. Rejections under 35 U.S.C. § 103

5.1 Claims 1-10, 12 and 13 are rejected as allegedly being obvious over Tamura *et al.* in view of Riechmann because Tamura discloses the MR16-1 monoclonal antibody and Riechmann discloses methods of humanizing and reshaping antibodies, and that it would be obvious to humanize MR16-1 utilizing the techniques of Riechmann. As discussed above, the claims to the pharmaceutical composition have been canceled and neither of the publications disclose administering to a subject a therapeutically effective amount of an antibody to an IL-6 receptor in a pharmaceutically acceptable carrier. Therefore, it is requested that this rejection be withdrawn.

5.2 Claims 1-14 are rejected as allegedly being obvious over Taetle *et al.* in view of Riechman because Taetle discloses the PM-1 monoclonal antibody and Riechmann discloses methods of humanizing and reshaping antibodies, and that it would be obvious to humanize PM-1 utilizing the techniques of Riechmann. As discussed above, the claims to the pharmaceutical composition have been canceled and neither of the publications disclose administering to a subject a therapeutically effective amount of an antibody to an IL-6 receptor in a pharmaceutically acceptable carrier. Therefore, it is requested that this rejection be withdrawn.

Conclusion

In light of the foregoing amendments, remarks and enclosed appendices, applicants submit that all claims are in condition for allowance, and they solicit an early indication to that effect. Should the examiner believe that further discussion of any remaining issues would advance the prosecution, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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